

## Varieties of Forgetfulness

November 12, 2022 Verdugo Hills Hospital Brain Health Forum

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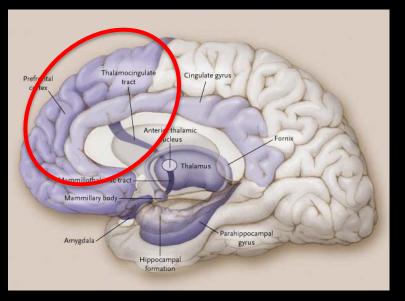
## Varieties of Forgetfulness

The Memory System

## The Spectrum of Forgetfulness

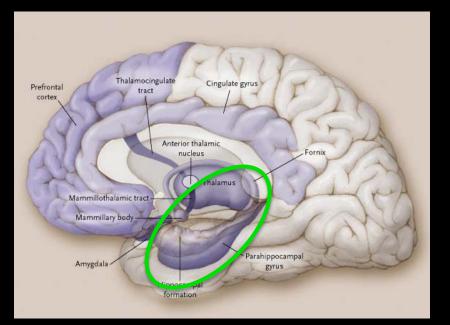
- Severity and Causes
- Prevention and Treatment

Working Memory – Prefrontal Cortex Holding small amounts of information in the span of conscious awareness



ATTENTION	Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order	[]21854
	μ.	Subject has to repeat them in the backward order	[]742
Read list of letters. Th	ne subject must tap with his hand	at each letter A. No points if $\geq 2$ errors	
		[ ] FBACMNAAJKLBAFAKDEA	AAJAMOFAAB
Serial 7 subtraction s	tarting at 100 [] 93	[]86 []79 []72	[]65
	(7) (m)	4 or 5 correct subtractions: <b>3 pts</b> , 2 or 3 correct: <b>2 pts</b> , 1 co	orrect: 1 pt, o correct: 0 pt

Budson A and Price B. N Engl J Med 2005;352:692-699 Luo L, Craik FI. La Revue Canadienne de psychiatrie 2008: 53: 346 Episodic Memory – Hippocampus Remembering events and experience that have happened to us personally



Remembering a short story, what you had for dinner last night, and what you did on your last birthday

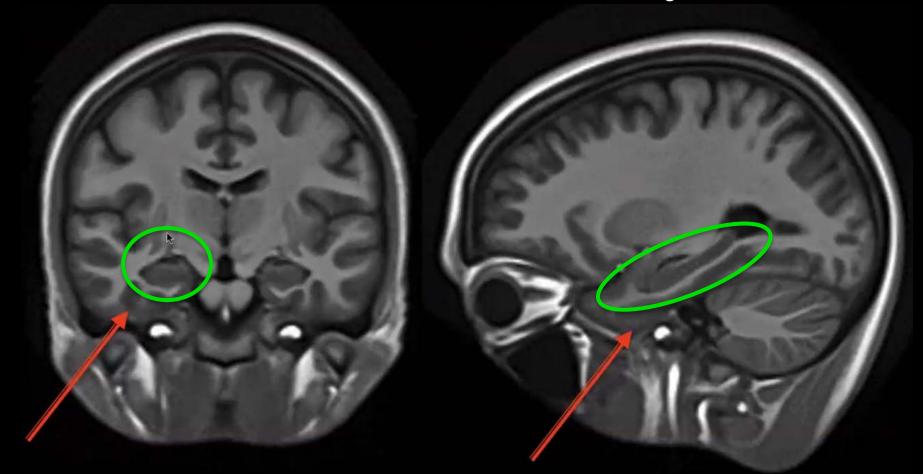
DELAYED RECALL	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only	/5
Optional	Category cue							
Optional	Multiple choice cue							

Budson A and Price B. N Engl J Med 2005;352:692-699 Luo L, Craik FI. La Revue Canadienne de psychiatrie 2008: 53: 346

## Hippocampus

**Coronal View** 

Sagittal View



7T MRI Mark and Betty Stevens Neuroimaging and Informatics Institute

## 3 R's to Remember

## 2. Record



## **1. Register 3. Retrieve**

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# **Causes of Forgetfulness**

#### Impair Registration/Retrieval

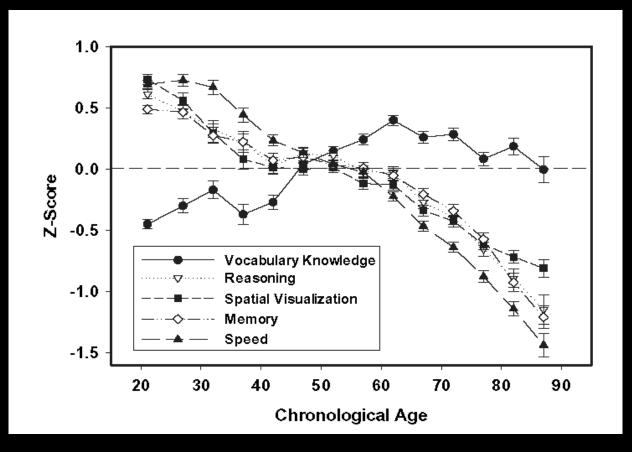
- Normal aging
- Side effects of medication
- Attention deficit disorder
- Obsessive compulsive disorder
- Depression
- Sleep deprivation
- Sleep apnea

#### **Impair Record Button**

- Alzheimer disease
- LATE (hippocampal sclerosis)
- Anoxic encephalopathy
- Herpes simplex encephalitis
- Wernicke Korsakoff syndrome (Thiamine deficiency)

LATE = limbic predominant, age-related, TDP-43, encephalopathy

#### Changes in Cognitive Abilities in Normal Aging

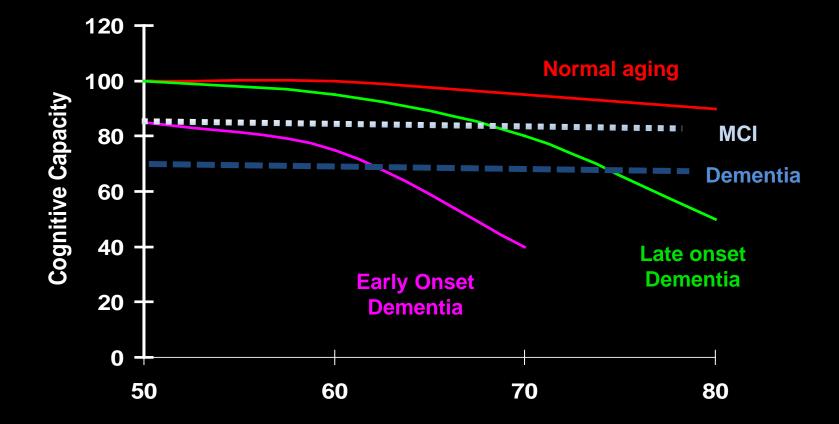


Salthouse, T.A. Nuerobiology of Aging 2009; 30: 507-514

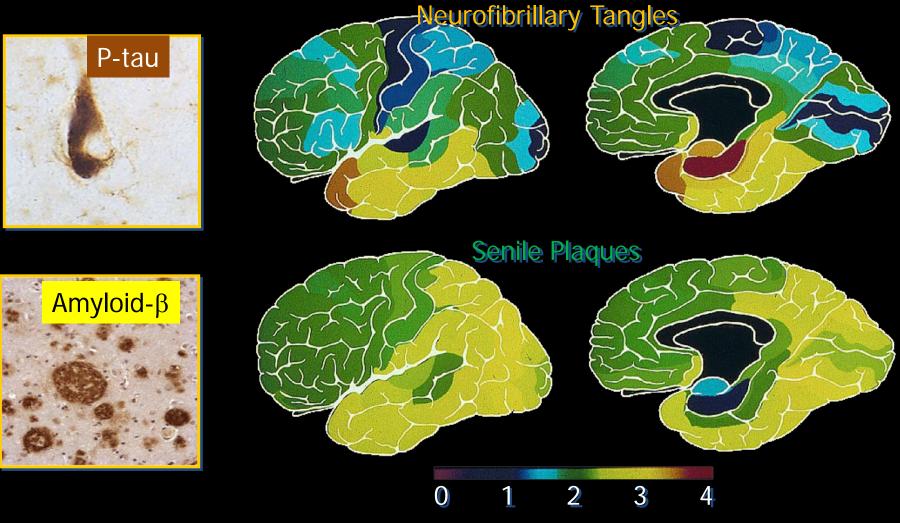
#### Changes in Cognitive Abilities in Normal Aging

Salthouse, T.A. Psychon Bull Rev 2016: 23: 932-939.

#### Slowly progressive decline in cognitive ability: Normal aging, mild cognitive impairment – dementia

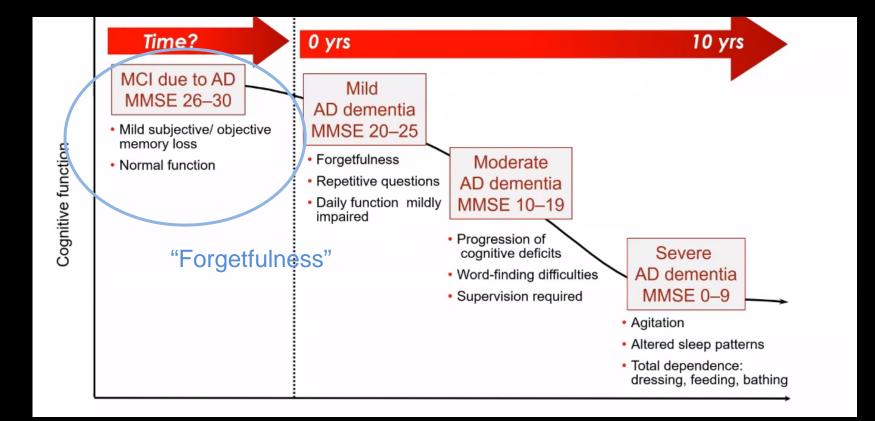


## Topographical Distribution of AD Lesions



Arnold et al. Cerebral Cortex. 1991;1:103-116.

# Symptomatic Progression of MCI and dementia due to Alzheimer Disease



**Courtesy Paul Aisen MD** 

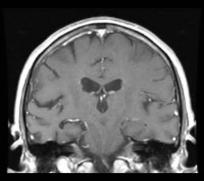
#### **Brain Imaging in the Diagnosis of AD**

#### **Clinical Diagnosis**

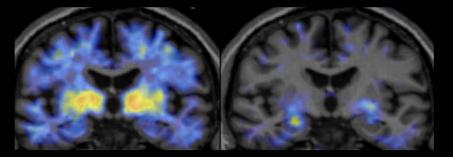
#### FDA-approved, but not paid by insurance

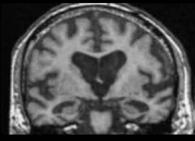
MRI

#### Amyloid PET Tau PET

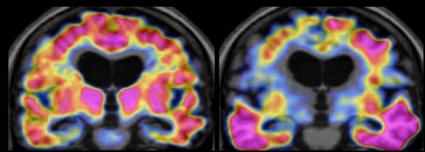


Normal





Dementia due to Alzheimer disease



β-Amyloid and p-tau proteins can also be measured in spinal fluid and blood. Johnson K. Ann Neurology 2016

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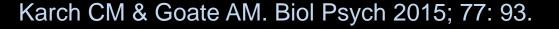
## **Prevention and Treatment**

- Prevention and Risk Reduction
  - Genes matter
  - Reduce modifiable risk factors
  - Adopt Healthy Lifestyle
    - Aerobic Exercise
    - Mediterranean diet
- Treatment for MCI or dementia due to "AD"
  - Symptomatic treatment
  - Disease-modifying treatment?

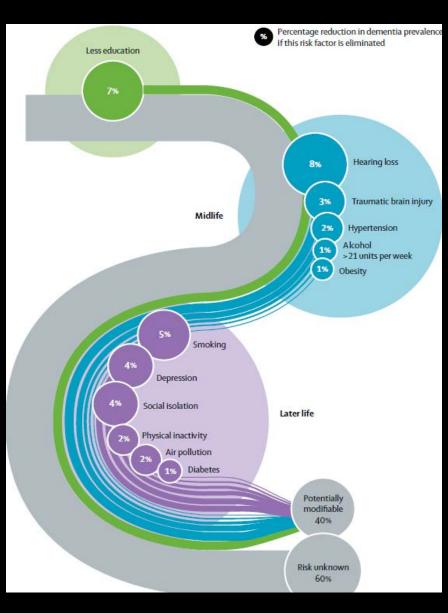
#### Genetic Risk for AD depends on frequency and strength of the allele



Apolipoprotein E4 accounts for the greatest genetic population attributable risk for AD



#### **12 Modifiable Risk factors for Dementia**



- Modifying risk factors might prevent or delay up to 40% of dementias
  - Hearing loss = 8%
  - Smoking = 5%
  - Social isolation = 4%
  - Depression = 4%
  - Hypertension = 2%
  - Physical inactivity = 2%
  - Diabetes = 1%

Livingston G et al. Lancet 2020;396:413-446.

## Commonly prescribed medications with cognitive side effects (Beers Criteria 2019)

Anti-cholinergics – urinary frequency Benzodiazepines – insomnia, anxiety "Z drugs" – insomnia

Anti-psychotics (1<sup>st</sup> generation) – hallucinations, confusion
 Anti-histamines (1<sup>st</sup> generation) – allergies
 Anti-depressants (1<sup>st</sup> generation) - depression, anxiety

J Am Geriatr Soc 2019; 67: 674-694

# AHA/ASA life's simple 7



#### Lifestyle modifications:

- 1. Smoking status
- 2. Physical activity
- 3. Weight
- 4. Diet
- 5. Blood glucose
- 6. Cholesterol
- 7. Blood pressure

Vivrani SS, Circulation 2020;141:e139-e596.

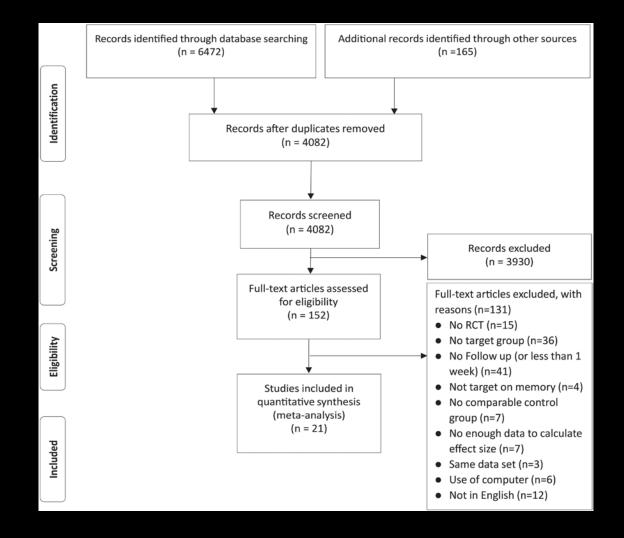
Factor	Ideal Definition
Smoking status	Nonsmoker
Physical activity	Moderate-intensity activity >150min/week or vigorous intensity activity >75min/week or combination
Body mass index (BMI)	<25 kg/m2
Diet	<ol> <li>Fruits and vegetables ≥ 4.5 cups/day</li> <li>Fish ≥ two 3.5oz servings/week (preferably oily fish)</li> <li>Fiber-rich whole grains (≥1.1g of fiber per 10g of carbohydrate) ≥ three 1oz equivalent servings/day</li> <li>Sodium &lt;1500mg/day</li> <li>Sugar sweetened beverages ≤ 450kcal (36oz)/week</li> </ol>
Fasting blood glucose	<100mg <dl (avoid="" hypoglycemia)<="" td=""></dl>
Total cholesterol	<200mg/dL
Hypertension	Untreated blood pressure <120/80 mmHg (avoid hypotension)

# **Mnemonic Training**

#### Strategies

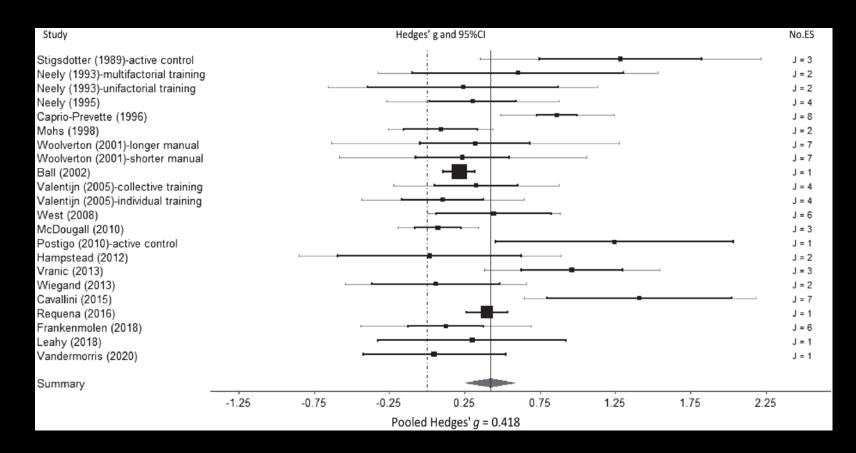
- Chunking semantic organization reduce memory load
- Loci associations based on well-established memory routes
  - learners to relate to-be-remembered information with such well-established routes during encoding so that they can mentally retrace their steps during retrieval (Yates, 2013).
- External strategies calendars and notes

#### Search for Studies that Qualify for Meta-Analysis



Chen, S. Psychology and Aging 2022.

#### Long Term Effects of Mnemonic Training in Normal Elderly Adults



#### Chen, S. Psychology and Aging 2022.

#### Effects of Cognitive Training in Normal Elderly Adults

			Memory		
Type of intervention	Control N (total)	Treated N	(total) Design		Estimate [95% CI]
Metacognitive					
Knowledge/Beliefs					
Caprio-Prevette & Fry, 1996 (9 effect	ots) -	56	Pre-Post, No control		0.65 [ 0.51, 0.79]
Lachman et al., 1992 (2 effects)	55	12	Pre-Post, Control	i	0.79 [ 0.39, 1.18]
Monitoring skills				1 1	
Bailey et al., 2010 (2 effects)	27	29	Pre-Post, Control	,⊢:■1,	0.09 [-0.24, 0.41]
McGuire, 2001 (1 effects)	20	21	Pre-Post, Control		0.13 [-0.33, 0.59]
- RE estimate for metacognitive training				-	0.52 [0.19, 0.84]
Strategic-Metacognitive					
Knowledge/Beliefs + Strategy					
Borella et al., 2012 (3 effects)	-	90	Pre-Post, No control		0.46 [ 0.34, 0.58]
De Beni et al., 2008 (2 effects)	-	133	Pre-Post, No control		0.79 [ 0.67, 0.91]
Fairchild & Scogin, 2010 (3 effects)	25	28	Pre-Post, Control	. <b>⊢</b> •	0.89 [ 0.51, 1.26]
Giuli et al., 2013 (1 effects)	-	61	Pre-Post, No control	∶⊢∎⊣	1.41 [ 1.14, 1.68]
Hohaus, 2007 (3 effects)	20	20	Pre-Post, Control	i   <b>-</b> ∎- ```	0.64 [ 0.27, 1.01]
Lachman et al., 1992 (2 effects)	55	12	Pre-Post, Control	: <b> </b>	0.54 [ 0.15, 0.92]
Lima-silva et al., 2010 (6 effects)	32	37	Pre-Post, Control		0.36 [ 0.11, 0.60]
Mohs et al., 1998 (2 effects)	74	68	Pre-Post, Control	-≡-1	0.06 [-0.14, 0.26]
Pearman et al., 2020 (4 effects)	20	33	Pre-Post, Control	<u> </u>	0.15 [-0.15, 0.45]
Scogin & Prohaska, 1992 (16 effect	ts) 47	22	Pre-Post, Control	<b>⊨</b> -1	0.16 [-0.15, 0.46]
Troyer, 2001 (3 effects)	24	36	Pre-Post, Control	í÷∎-í	0.12 [-0.18, 0.41]
Vranic et al., 2013 (6 effects)	20	31	Pre-Post, Control	· · · ·	0.92 [ 0.60, 1.23]
Yassuda, 1999 (4 effects)	44	23	Pre-Post, Control	⊢∎∔  ' '	-0.20 [-0.48, 0.07]
Monitoring skills + Strategy					
Bottiroli et al., 2013a (5 effects)	36	38	Pre-Post, Control	┝╼┤	0.48 [ 0.23, 0.72]
Bottiroli et al., 2013b (5 effects)	33	39	Pre-Post, Control	: [-∎-[	0.44 [ 0.20, 0.69]
Bottiroli et al., 2017 (6 effects)	31	30	Pre-Post, Control	i ⊨∎-1	0.39 [ 0.13, 0.64]
Cavallini et al., 2008 (11 effects)	28	34	Pre-Post, Control	: <b> </b>	0.51 [ 0.14, 0.88]
Cavallini et al., 2010 (12 effects)	57	58	Pre-Post, Control	:  - <b>-</b> -  '	0.44 [ 0.19, 0.70]
Cavallini et al., 2015 (8 effects)	16	18	Pre-Post, Control	i''	- 1.81 [ 1.34, 2.28]
Dunlosky et al., 2003 (4 effects)	31	33	Pre-Post, Control	: <b>⊢</b> ∎-1	0.41 [ 0.14, 0.68]
Lachman et al., 1992 (2 effects)	55	12	Pre-Post, Control	<b>⊢</b> ∎_	0.38 [-0.00, 0.77]
McGuire, 2001 (1 effects)	20	23	Pre-Post, Control		-0.01 [-0.46, 0.44]
- RE estimate for strategic-metacognitiv					0.44 [0.29, 0.58]
				Ť	,
					2 2.5
			Standardiz	zed Mean Difference (aggreg	ated by study)

Sella, E. Aging and Mental Health 2022; 10/12/1-12.

## Effect of Physical Exercise on Global Cognition in Mild Cognitive Impairment

Biazus-Sehn. Arch Gero Geriatr 2020; 89: 104048

## Medication that Increase Acetylcholine 12-month treatment effects

Donepezil (10 mg)				
Mohs, 2001	<b>n</b>			0.72 [-1.29, 2.73]
Winblad, 2001	-			1.90 [ 0.51, 3.29]
Subtotal (95% Cl), <i>l</i> ² = 0%				1.52 [ 0.38, 2.66]
Galantamine				
Hager, 2014	- <b>-</b> -	ł		0.58 [ 0.27, 0.90]
Subtotal (95% Cl), <i>l</i> ² = 0%	-			0.58 [ 0.27, 0.90]
Rivastigmine				
Karaman, 2005		H		1.40 [ 1.12, 1.68]
Subtotal (95% Cl), I² = 0%		•		1.40 [ 1.12, 1.68]
Overall (95% CI), <i>I</i> ² = 79.0%		-		1.10 [ 0.48, 1.72]
	0	2	l 	

**Fig. 5.** Forest plot showing the treatment effects from the individual trials and meta-analysis results for acetylcholinesterase inhibitors at 12 months after treatment initiation. For the reference numbers of the studies, please refer to Table 1.

#### Knight R, Dementia Geriatric Cognititve Disorders 2018; 45: 131



The University of Southern California Memory and Aging Center www.brainhealth.usc.edu

NIA Alzheimer Disease Research Center (ADRC) California Alzheimer Disease Centers (CADC)





USC Health Care Consultation Center 1520 San Pablo Street Los Angeles, CA Rancho Los Amigos National Rehabilitation Center 7601 East Imperial Highway Downey, CA